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10/038,060	01/04/2002	Andrew Koff	14538A-005111US	5760

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,060	KOFF ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sh et with th correspondenc addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9/3/02 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This application is a continuation of 08/973,823.

2. Claims 1-11 are pending and under consideration.

Specification

3. The disclosure is objected to because of the following informalities: The specification contains figures labeled Figures 1B1-1B2, C1-D4, D1-D4; 4A1-A3, B1-B-3; 5A1-A6; 7A1-A3 and B1-B3. However, the section the specification on brief description of figures does not describe different panels of these figures. Applicants are required to describe different figures completely.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the proliferation of thymocytes in a transgenic mouse, comprising altering the endogenous gene encoding p27kip1 of the mouse in the somatic and germ cells of the transgenic mouse, wherein the transgenic mouse does not produce a functional p27kp1, wherein the p27kip gene is altered by inserting a nucleotide sequence encoding a positive selectable maker in the endogenous p27kip1 gene, mutation or deletion of the endogenous p27kip1 gene, wherein the transgenic mouse is produced by introducing a plasmid in mouse ES cells and injecting the mouse embryonic ES cells into a blastocyst stage embryo, wherein the plasmid comprises, a p27kip1 gene altered by inserting the nucleotide sequence encoding the positive selectable marker and a nucleotide sequence encoding a negative selectable marker such that

the distance between the nucleotide sequence encoding the negative selectable marker and the p27kip1 gene allows homologous recombination between the altered p27kip1 gene in the plasmid and the endogenous p27kip1 gene present in the genome of the mouse ES cells, does not reasonably provide enablement for other embodiments of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

When broadly interpreted, the claimed invention would encompass altering the p27kip1 gene in any and all somatic cells of a non-human animal by any and all methods such that there is increased proliferation of thymocytes in the non-human animal. Furthermore, the claimed invention would encompass practicing the method in any and all non-human animals. However, the specification as filed does not provide sufficient guidance, working examples and evidence as to how an artisan of

skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation as discussed below.

The specification as filed discloses a knock out transgenic mouse wherein the endogenous p27kip1 gene of the mouse has been altered by homologous recombination such that no functional p27kip1 protein is produced (page 26, lines 15-37 continued on page 27, lines 1-4). The mouse has increased body weight, general increase in organ weights but the increase in organ weight was observed most in spleen and thymus (see pages 28 and 29). an increase in the number of splenic T cells, and an increase in the number of thymocytes (see pages 31-33). The specification on page 14 of the specification in lines 15-30 discloses that the altered gene can be introduced either at a developmental stage or after the animal is born by introducing the altered genes in the somatic cells of the animal, for example using viruses, vectors, liposomes to produce a recombinant non-human animal.

First, the instantly presented claim 1 when broadly interpreted would mean that if p27kip1 is altered in any one somatic cell or any one somatic cell type of a non-human animal, would result in an increased proliferation, however, the specification does not teach as to how lack of p27kip1 in one cell type only would result in the increase in the proliferation of thymocytes, however, there is no teaching in the specification or in the prior art that suggests that inhibiting p27kip1 in any cell of an animal would result in an increased proliferation of a cell of another unrelated organ. If the p27kip1 was inhibited in skin or in bone marrow, thymocyte proliferation will increase in thymus. The prior art at the time of the invention noted that p27kip1 is an inhibitor of the activation of G1 cyclin/CDK complexes and this blocks the entry of a cell in S phase (see Koff and Roberts 1995 in Cell cycle Research, exhibit 4 of the IDS), however, there is no evidence that increasing the level of p27kip1 in one cell results in the block of a cell in another organ. In the absence of any teaching that altering the level of p27 in one somatic cell in one organ in an animal would alter the proliferation of another somatic cell in another organ, an artisan would not know how to practice a method for there is not sound scientific basis in the specification or in the prior art and therefore, would require

extensive experimentation to first establish the principal that inhibition of p27kip1 in one organ of the body results in an increased proliferation of the cells of another organ of the body.

Next the question is can one increase proliferation of thymocytes in vivo by inhibiting p27kip1 in thymus gland? It is noted that the specification discloses that the proliferation of thymic T cells in an animal can be increased by exposing the animal with different agents capable of inhibiting the function of p27kip1 and that in one embodiment the agent is an antibody, however, the specification does not teach as to how an artisan would have administered an antibody to an animal such that the gene encoding p27kip1 in the thymus gland would be altered such that functional p27kip1 would be decreased creating a deficiency of p27kip1 and increase in proliferation of thymocytes. It is noted that while the phenomenon of blocking the activity of a protein by binding a specific antibody (directed against the protein) to the protein is known in vitro, Examiner could not find an example, wherein administration of an antibody caused a mutation or deletion of alteration in the structure of a gene such that a functional protein encoded by the gene is not produced. The specification does not teach any steps of the method wherein an antibody would be administered to an animal, what would be the doses, what route of administration will be used, and how would the change in the proliferation of the thymoctyes would be monitored. It is noted that an artisan would have to carry out extensive experimentation to alter the p27kip1 in the thymus gland or bone marrow in vivo and such would require undue experimentation because neither the specification nor the prior art teaches such a method.

In case the altered gene is introduced in the cell of an animal after the animal is born, the specification is not enabling because the specification does not provided any guidance as to how the method would be carried out. The specification is not enabling for introducing the altered gene in the thymocytes or bone marrow because the art of gene delivery in vivo to a particular cell type and also in general is highly unpredictable and because the specification does not provide suitable guidance as to how an artisan would have dealt with uncertainties and problems recognized in the art regarding the unpredictability of gene delivery

as discussed below. The art of targeting expression of a polynucleotide to a particular cell or tissue is unpredictable because numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al (FASEB J. 9:190-199, 1995) discussed the state of the art of targeted vectors for gene therapy and noted that there is requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells in vivo or ex vivo and that that these systems should be efficient and accurate. They further stressed that the range of different diseases means that no single delivery system is likely to be universally acceptable and that the stringency with which the therapeutic genes need to be accurately delivered could greatly vary, for example, a vector system used for gene delivery in cystic fibrosis tissue would not be suitable for cancer gene therapy (see first paragraph in column 1 on page 190). Likewise, Deonarain (Deonarain MP. Exp. Opin. Ther. Patents. 8:53-69, 1998) also noted that gene delivery remains the major technological stumbling block in gene therapy strategies. Deonarain further noted that there are several drawbacks of different targeting vectors, such as, risk of secondary malignancies due to integrated vectors, recombination of disabled viruses to produce infective virus, lack of cell specificity, lack of infection of non-dividing cells by retrovirus, inactivation and inactivation of the viral vectors by host complement (see column 1 continued in column 2 on page 54). In the instant case, an artisan would have to

target the expression of the altered p27kip1 gene to thymocytes or bone marrow and the specification does not teach what vectors would target the gene or the plasmid carrying the gene to thymocytes and how would an artisan deal with the issues discussed above. It is noted that although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for gene delivery in specific examples, gene delivery as a broad-based art is clearly unpredictable.

Next, if one had to assume that the p27kip1 in a cell is altered first in vitro and the cell is administered, it is noted that the method of ex vivo therapy is also unpredictable. For example, some of the issue of cell therapy are: source of the cells is an important determinant and the specification does not provide any guidance whether autologous, xenogeneic or allogeneic cells would be used in the method and how would the immunological issues would be dealt with if non-autologouse cells are used. Next the issue is: how would the cells be administered to the animal and what doses would be used. It is noted that the specification does not provide any guidance as to how ex vivo method encompassed by the claimed invention would have been practiced.

If one had to assume that the claimed method involves making of knockout transgenic non-human animals, it is noted that making of transgenic non-human animals is unpredictable as recognized in the prior art at the time of the invention as discussed below. As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. Investigators observed 5-70 fold lower yields of a recombinant protein in transgenic mice when they used a construct designed for expression in sheep (see lines 1-12 in 4th para of col 1 on page 632 in Mullins et al. (Mullins JJ et al. Hypertension 22:630-633,1993)). The variation in expression levels between different cell lines and species may be attributed to host genetic

background, the site of chromosomal insertion and absence of specific transcription factors.

In a more recent assessment of the transgenic technology, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

Introduction of foreign DNA into fertilized oocyte , for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will express the transgene to a level high enough so as to enable the development of the claimed phenotype in the transgenic animals.

In addition to the limitation of making transgenic animals, the art of culturing and maintaining ES cells in culture was also unpredictable at the time of the invention. Gardner and Brook (Gardner RL and Brook FA. International J. of Dev. Biol. 41:235-243, 1997) summarized the progress in the field of ES cell biology, "Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most stains have so far proved refractory to the derivation of cell lines....."

Additionally, gene targeting and selection of the ES cells that harbor the integration of a desired construct also has been shown to be unpredictable in animals other than mice. To prevent their differentiation, ES cells are maintained in culture in the presence of mouse derived factors that inhibit differentiation either by coculturing the cells in the presence of feeder cell lines or by adding agents to the culture as a media supplement. However, it has been suggested that the such differentiation-inhibitory derived from mouse do not adequately prevent differentiation of stem cells in species other than the mouse. For example, rat ES cells, capable of producing chimeras, grow best on primary rat embryonic fibroblasts as the feeder layer (see last para in col 1 on page 1558 in Mullins and Mullins, 1996) (Mullins LJ and Mullins JJ. J. Clin. Invest.97:1557-1560, 1996).

Furthermore, the art of transgenesis based on ES cells is unpredictable. The steps of producing a knockout mouse include, isolating the gene from a mouse genomic library, destroying the gene by inserting therein a selectable marker gene, introducing vectors incorporated with the destroyed gene into cultured ES cells thereby allowing homologous recombination to occur, isolating and identifying a clone in which homologous recombination has been effected, injecting the clone into a blastocyst that develops into the desired mouse. While the steps to produce knock out mouse have been well developed and used in mice, they have not been fully developed in other animals, particularly the art of gene targeting in ES cells and culture and selection of the ES cells that harbor the desired integration has been shown to be unpredictable in animals other than mice. Mullins and Mullins (1996) stated "However, at the present time the reliable generation of bovine ES cell lines requires the pooling of inner cell mass from several blastocysts and further efforts are required to enable the long term culture of clonal bovine ES cells. Although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has the germline transmission of an ES cell has been successfully demonstrated " (Page 1558, para 1 in col 2).

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue

amount of experimentation to make and use any and all transgenic non-human animals wherein the endogenous p27kip1 gene of the somatic and germ cells would be deleted or mutated such that functional p27kip1 was not produced in the somatic and germ cells of the trangenic non-human animals. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

6. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. When given broadest interpretation, claimed method would encompass transgenic knockout non-human animals wherein the endogenous p27kip1 gene of the transgenic animals has been inactivated such that functional p27kip1 is not produced. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In this case, the specification provides example and methodology to make knock out mouse (see pages 20-21). However, considering the fact that the claimed invention encompasses transgenic knockout animals whose phenotypes and characteristics may not be known because the art of making transgenic animals or knockout animals is highly unpredictable. It is noted that it is well known in the art that there is unpredictability of phenotypic effects caused by variation in the genetic background used to generate or propagate gene targeted models and there are many examples in which animals containing same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse gene backgrounds, demonstrating that genes unrelated,

per se, to the ones being targeted can play a significant role in the observed phenotype (see the abstract in Sigmund CD. Arterioscler. Thromb. Vasc. Biol. 20:1425-1429, 2000).

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of inactivating a gene can not be predicted, particularly when a gene product may be interacting with the proteins of a family of proteins. For example, Korach et al (US Patent No. 5,650550) produced a knockout mice lacking a functional estrogen receptor. One skilled in the art would not have predicted that such an animal would even be viable (see col 9, lines 22-39), much less have been able to predict the resulting phenotype. In the instant application, what would have been the result of the inactivating p27kip1 gene in the transgenic non-human animals encompassed by the invention, can not be predicted. With the limited information disclosed in the specification, an artisan would have not been able to predict whether all these animals would have had same or different phenotypes compared to the knockout mice or transgenic mice.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite because it recites the phrase "the gene encoding p27kip1 is altered by insertion of a positively selectable marker". It is noted that a marker is usually a protein and it is unclear as to how a protein would be inserted in the gene encoding p27kip1.

Claim 1 is indefinite because it recites the term "the gene encoding p27kip1 in a somatic cell." It is noted that when broadly interpreted a somatic cell could contain a gene encoding p27kip1 in a plasmid in addition to the endogenous gene of the somatic cell. It is unclear as to which gene is intended to be recited in the instant case. Applicants are advised to use the term "the endogenous gene encoding p27kip1". Furthermore, regarding claim 14 it is unclear whether the p27kip1 gene is altered in only one somatic cell of the animal or in all the somatic cells of the animal.

As noted in claim 1, claim 9 is also indefinite because it recites the term "a gene encoding p27kip1 in a the cell." It is noted that when broadly interpreted a somatic cell could contain a gene encoding p27kip1 in a plasmid in addition to the endogenous gene of the somatic cell. Applicants are advised to use the term "the endogenous gene encoding p27kip1".

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 1-11 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Roberts JM et al (US Patent No 5,958,769, dated 8-28-99, filing date 1-18-1996).

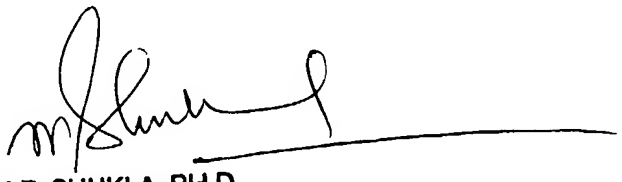
Roberts et al teaches the method of making a transgenic mouse wherein the endogenous p27 gene of the mouse was inactivated by inserting a plasmid that

comprised a neo gene and a HSV TK gene. The plasmid was linearized and transfected by electroporation into mouse ES cells and the transfected ES cells comprising the inactivated p27 gene were injected into blastocysts to produce transgenic mice. Homozygous transgenic mice showed on average about 30% increase in body weight. The thymus and spleen of these mice were of almost the twice compared to controls and the increase in size was due to hypercellularity of these tissues (see lines 30-37 in column 19).

Accordingly, the invention of claims 1-11 is clearly anticipated by Roberts et al.

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

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Art Unit 1632